REMARKS/ARGUMENTS

Claims 17, 32, 33 and 40-46 are pending and presented for examination. Claim 17 has been canceled. Claims 45 and 46 are newly presented. After entry of these amendments, claims 17, 33, and 40-46 will be pending.

Claims 17, 31, 32, and 40-44 stand rejected under 35 U.S.C. §112, first paragraph for an alleged lack of enablement. Applicants respond to this rejection below.

Support for Amendments to the Claims

For purposes of clarity, claim 17 has been amended to also set forth "an inactivated form" of the virus. Support for this subject matter is as set forth previously for the subject matter of claim 32 and is found *inter alia* in the specification in the paragraphs bridging pages 9 and 10.

New claims 45 and 46 depend from claim 32 and set forth the virus is HIV-1 or HIV-2 respectively. Support for this subject matter is found *inter alia* in the specification at p. 19, lines 16-20.

In view of the above, the Applicants believe the amendments to the base claim adds no new matter and respectfully request their entry.

Response to the Rejection for An Alleged Lack of Enablement

Applicants respond to each of the issues identified by the Examiner in turn.

A. Nature of A Protective or Therapeutic Immune Response.

Applicants submit that a protective or therapeutic immune response is not limited to a sterilizing immunity preventing an infection upon later exposure to the virus. A protective or therapeutic immune response encompasses a protective immunity allowing only a transient infection to be established upon exposure, a protective immunity limiting the severity or progression of the diseases, or a protective immunity reducing the secondary transmission of

virus to others. Applicants claimed methods need not only provide a complete or sterilizing immunity to be useful and enabled. A recognized goal of vaccines is to prevent disease, not necessarily infection. See, also Cohen, *Science* 262:1820 (1993) which is already of record.

B. *The Predictive Value of the SIV Macaque Model Generally*

The present rejection is largely based upon the contention that the SIV/macaque model is not a suitable model for HIV infection and vaccination in the human. To support this contention, the Action states at page 3, lines 26-31:

> The inventors report that the invention is predicated upon the finding that the low dose administration of an SIV immunogen leads to a strong and long-term protective cell-mediate immune response. However, as set forth below (see point 4), SIV is not an art-recognized animal model for HIV-1 or -2 vaccine development. Thus, any findings from such studies can not be extrapolated to HIV and humans.

Point 4 in turn cites Hoth et al. (1994); Stott and Almond (1995); Graham and Wright (1995); Haynes et al. (1996); Haynes (1996); Kent et al. (1997); Lee (1997); Letvin (1998); Burton and Moore (1998); Moore and Burton (1999); Nathanson and Mathieson (2000); and Johnston (2000); Bende and Johnston (2000) and Feinberg and Moore (2002). As Point 4 does not individually cite any of the above references for any teaching in particular, Applicants necessarily address each reference:

Upon review, Applicants have found that the cited references DO NOT support the contention that the SIV/macaque model is not predictive. In fact, many of the cited references unambiguously treat the SIV macaque model as being generally quite predictive:

When addressing Preclinical Vaccine Research in primates, Hoth et al.(1994) discuss both the chimpanzee HIV infection model and the SIV macaque model. Nowhere do Hoth et al. opine or suggest that the macaque model is not a suitable model. In fact, Hoth et al. state:

> It has been suggested that infection of monkeys with simian immunodeficiency virus strains that induce a slower onset of of disease may be more relevant than any model widely used in HIV research. It is interesting to note that recombinant

> approaches have proved effective in at least one experiment that used the slower simian immunodeficiency virus model (19).

(see p. 604, last two sentences of last full paragraph of first column). Later, Hoth et al. further state

> When a short-term model for simian immunodeficiency virus infection and disease is used, the attenuated virus vaccine has provided the most impressive protection (23). . . . It should possible to take full advantage of this model to derive insights on correlates of protection.

(see p. 604, first paragraph, second column).

The Stott and Almond (1995) reference specifically assesses animal models of AIDS. This reference is absolutely contrary to the Action's contention as well. Stott and Almond state in the last sentence of their article:

> In the meantime, our own bias on the evidence so far, is that infection of macaques with SIV or HIV-2 will prove to be the most rewarding and reliable model for the pathogenesis and prevention of AIDS.

Letvin (1998) states in the section titled "Animal Models for Assessing HIV-1 Vaccine Strategies" that

> "the SIV-infected macaque has been a crucial model for assessing HIV-1 vaccine strategies over the past decade."

(see p. 1876, middle column, last sentence of first paragraph). The quoted section then goes on to discuss some of the similarities and differences between the model and target systems and concludes:

> However, the variety of models available affords an important opportunity to assess vaccine strategies in a number of different systems and thus gauge the potency of a particular vaccine-elicited immunity in preventing AIDS infections.

Bende and Johnston (2000) state that

> While there is no practical model for HIV infection, there are good animal models of HIV/AIDS, namely SIV and simian HIV (SHIV) infection in monkeys. SIV infection has numerous similarities to HIV infection in humans.

(see page 536, first column, second sentence under heading "Animal models."

Nathanson and Mathieson (2000) state:

> The parallel between human and animal studies of nef-deleted mutants of SIV have strengthened confidence that SIV can be used as a model for HIV attenuation. However, these observations have had a chilling effect on the outlook for a safe, attenuated HIV strain that replicates sufficiently to be an effective immunogen.

(see page 580, first column, second full paragraph).

The Johnston (2000) reference discusses the biology of various animal models, including the macaque. This reference emphasizes the value of the macaque model and concludes that

> Evaluation of vaccines in HIV/AIDS animal models is an essential component of a comprehensive vaccine research and development program. Improvements that could be made in the macaque model include (1) selecting viruses that infect by mucosal routes and that share an early course of infection and replication kinetics in common with HIV; (2) using SHIV isolates to address clade issues; (3) selecting or breeding animals that are well characterized and as homogeneous as possible in immune response genes; (4) expanding and adapting more sensitive and quantitative assays; and (5) conducting comparative studies of vaccine approaches.

Two references caveat their affirmation of the SIV macaque model by noting that the SIV and HIV structural differences (e.g., envelope proteins) differ so as to prevent a direct applicability of an SIV vaccine to HIV:

Graham and Wright (1995) state:

> SIV can infect macaque monkeys and cause an AIDS-like illness. The system is a legitimate model for retrovirus induced AIDS and is valuable as a tool with which to study pathogenesis and vaccine strategies. However, structural differences between SIV and HIV complicate the direct translation to humans of the vaccine studies in the SIV-macaque system.

(see page 1333, paragraph under heading "Animal Models").

Lee (1997) observes that

> The pathogenesis of SIV in rhesus macaques mirrors that observed with HIV. However, SIV-encoded proteins differ in antigenicity and immunogenicity from HIV, raising the question

> of immediate applicability of any successful SIV vaccine design.

(see page 609, column 2, last two sentences of first full paragraph).

Several references were not particularly edifying with respect to the issue at hand. The references of Kent et al. (1997), Haynes (1996), and Moore and Burton (1999) do not appear to address the predictive value of the SIV macaque model. In addition, the Burton and Moore (1998) rather cryptically simply stated in the last paragraph of their reference *"Animal models need rationalizing but remain of central importance."* Feinberg and Moore (2002) conclude their review with the following relatively neutral statement:

> Animal models cannot determine whether a vaccine will be effective against HIV-1 infection of humans, only Phase III clinical trials in humans can do so. However, challenge experiments in the macaque models can potentially add important insights to those gained in Phase I and Phase II studies in humans, and they should meaningfully inform decisions that will impact many thousands of volunteers and involve many millions of dollars. To be most informative and helpful, challenge studies in macaques should now seek to resolve the most difficult issues in AIDS vaccine development and, depending, on the nature of the scientific question under evaluation, studies may need to use more than a single challenge virus. Within this context, it is essential that macaque models be improved so as to mimic, as closely as possible, the actual circumstances of HIV-1 infection and transmission in humans.

Only one reference, Haynes et al. (1996), is fairly construed in accordance with the Action's contention that the SIV macaque model is not predictive. This references states that

> Current animal models of either SIV or simian immunodeficiency virus (SIV) fall short of precisely mirroring human HIV infection. … lacking animal models researchers must turn toward human clinical trials to answer many of the difficult questions about HIV pathogenesis and HIV vaccine development.

However, the Haynes (1996) reference is also particularly sparse as to the factual basis for its assertion.

C. *The Predictive Relevance of the SIV/Macaque Model with Respect to the Claimed Subject Matter*

The base claim as amended recites:

A method for vaccinating a human against a human immunodeficiency virus comprising the step of:
administering to said human an amount of an immunogen comprising an attenuated form or inactivated form of said human immunodeficiency virus sufficient to induce a cell mediated response against said human immunodeficiency virus but below the amount necessary to induce an offsetting humoral response to said human immunodeficiency virus.

As noted in the specification in the paragraph bridging pages 3 and 4, Applicants have found through their work in macaques with a virus related to HIV, the simian immunodeficiency virus ("SIV"), that administration of high doses of SIV to macaques results in infection and antibody production with minimal cell-mediated immunity. By contrast, administration of lower doses elicits strong and long-term protective cell-mediated immunity with neither antibody production nor detectable infection [see, for instance, M. Clerici et al., IX International Conference on AIDS (Berlin, 7 to 11 June, 1993), abstract 3279, already of record and enclosed].

Applicants note the Examiner's concern that findings from the SIV/macaque model can not be extrapolated directly to HIV and humans. As a threshold matter, Applicants would like to make clear that the SIV macaque model is not being relied upon to support the selection of the particular HIV immunogen itself. Applicants appreciate there are differences in the antigenic determinants of these otherwise closely related diseases.

With respect to the predictive value of the SIV/macaque model for the claimed subject matter, Applicants call the Examiner's attention to the Affidavit of Dr. Raoul Benveniste which is submitted herewith. This Affidavit greatly expands the evidentiary support demonstrating 1) the SIV macaque model is an excellent model for HIV disease and pathogenesis; 2) that low, non-infectious doses of SIV elicit a long-lasting protective T-cell mediated immune responses; and 3) that epidemiological and clinical studies support that non-infectious doses of HIV can similarly elicit protective T-cell mediated immune responses in the human. Applicants respectfully request the Examiner reconsider the predictive value of the SIV macaque model in view of the Affidavit.

D. Guidance as to the Induction of a Cell-Mediated Immune Response Without Inducing A Noticeable Humoral Response.

The Action alleges several factors (e.g,. immunogen dose, adjuvant selection, route of immunization, structure of the immunogen, type of the antigen presenting cell, costimulatory signals, vaccinee genetic background, cytokine environment, vacinee immunologic status) as rendering the immunization process empirical.

With respect to immunogen dose and adjuvant selection, virtually all dose response/formulation is "empirical at best." Indeed, the Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988). Here, as noted in the Affidavit, Applicants have found that subinfectious amounts of an immunogen can induce a *protective* cell-mediated immune response which is not associated with a humoral immune response over a thousand-fold range of sub-infectious dosages (see Clerici et al. AIDS 8:1391 (1994)). In view particularly of the teachings of the specification at p. 13, and the Applicants disclosure of the wide dosage ranges operable in the macaque (see Clerici et al. Abstract presented at the June 1993 Berlin Conference (already of record), finding a suitable dosage regimen would be mere routine for one of ordinary skill.

With respect to route of immunization, Applicants note that the macaque models cited in the Affidavit successfully used both intravenous and mucosal routes of administration.

With respect to vaccinee genetic background, the cytokine environment, and the antigen presenting cells, the methods are robust. Applicants note that the macaques are a highly variable, genetically heterogeneous population and that such variability has not prevented the methods for working for a substantial proportion of the subject populations. Indeed, the effects, as set forth in the Affidavit, have been seen in two distinctly different species of macaque: the pig-tailed macaque and the cynomologous macaque. Nor, indeed, has it prevented the macaque

model from robustly predicting a similar effect in humans as subsequently evidenced in various epidemiological studies as set forth in the Affidavit. Applicants further note that the presence of some inoperable embodiments within the scope of the claim is not a bar to patentability[1]

With respect to variability of HIV, Applicants note that Fowke et al. have shown HIV resistance is found in a population of prostitutes exposed to a many HIV variants.

E. Alleged failure to disclose suitable HIV-1 and HIV-2 immunogens.

As amended, the base claim now sets forth an immunogen comprising an attenuated or inactivated form of human immunodeficiency virus. Such viruses include those wherein the human immunodeficiency virus has been inactivated by removing a sufficient portion of its genetic material so as to render it incapable of replicating. The specification teaches several such immunogens (e.g., nef and gag mutants) which have been so inactivated at page 10. In addition, the specification exemplifies methods for attenuating a virus in the paragraph bridging pages 9 and 10 and Example 1. Pursuant to MPEP §2164.01, a patent application does not need to teach, and preferably omits, what is well known to one of ordinary skill in the art. Attenuated and whole inactivated vaccine HIV immunogens were known in the art at the time of filing (see, generally, Hoth et al, p. 604, first sentence, second full paragraph, first column; see also, with respect to *gag*, Gorelick RJ et al. *J Virol.* 1990 Jul;64(7):3207-11 (enclosed); and see with respect to *nef* deletions, Kestler et al. *Cell* 65:651 (1991), of record).

F. Absence of Working Embodiments

The specification does not provide a working embodiment of the claimed methods in humans. However, the specification does describe the operability of the method in the SIV macaque model. More importantly, the subsequent epidemiological and clinical studies as set

[1]MPEP § 2164.08(b) Inoperative Subject Matter
The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. Rev. 1, Feb. 2003 2100-192

forth in the Affidavit provide substantial evidence that the claimed method would work in the human for HIV.

G. State of the Art of HIV Vaccine Development

The epidemiological studies set forth in the Affidavit show that even in the face of the quasispecies nature of HIV, the potential for an immune escape, the ability of the virus to reside quiescently in lymphocytes, the alleged lack of understanding of the correlates of such protective immunity, and the alleged lack of understanding of the mucosal immune responses, a protective immunity is, in fact, realized. The macaque data is in accord with and can explain these subsequent epidemiological findings.

A specification need not teach how a claimed method operates to produce a desired result as long as in fact the claimed methods do operate to provide the result. Here, patentability simply does not require that the specification resolve the general considerations identified by the Examiner which appear to be readily overcome. The macaque and epidemiological data thus render these considerations moot with respect to the patentability of the claimed subject matter.

H. Breadth of the Claims

The breadth of the claims is commensurate with the breadth of the disclosure. The specification teaches that administering dosages of the immunogens comprising an attenuated or inactivated form of HIV which dosage is too small to induce a humoral immune response against HIV but large enough to induce a cell-mediated immune response against HIV can protect against subsequent HIV infection. The breadth of the claims is fairly commensurate with the findings in the macaque model and also fairly supported by the subsequent epidemiological findings.

Thus, in light of the above, Applicants submit that it would not require undue experimentation for the skilled artisan to practice the claimed invention. Applicants thus respectfully request that the above rejection be reconsidered and withdrawn..

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

Frank J. Mycroft
Reg. No. 46,946

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
FJM:fjm
60184967 v1